UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

DATE: **26-June-2014**

SUBJECT: **Cyphenothrin Residential Application/Post Application Biomonitoring Study**: Secondary Review of Cyphenothrin; Gokilaht; "An Observational Biological Monitoring Study for Measurement of Human Exposure to Cyphenothrin During and Following Application of Sergeant's Gold® Flea & Tick Squeeze-On for Dogs

PC Code: 129013
Decision No.: 458169
Petition No.: NA
Risk Assessment Type: Occupational/Residential Exposure Assessment
TXR No.: NA
MRID No.: 48601301

DP Barcode: D396437
Registration No.: 2517-80
Regulatory Action: Section 3
Case No.:
CAS No.: 39515-40-7
40 CFR: §180.

FROM: Jeff Evans, Environmental Scientist
Chemistry and Exposure Branch
Health Effects Division, 7509P

THROUGH: David J. Miller, Branch Chief
Chemistry and Exposure Branch
Health Effects Division, 7509P

David J Miller 26-JUN-2014

TO: Driss Benmhend, Biologist
Insecticide Branch
Registration Division, 7505P

Christina Swatrz, Chief
Risk Assessment Branch II
Health Effects Division, 7509P

ACTION REQUESTED:
The Registration Division requested that the Health Effects Division (HED) conduct a review of biological monitoring study addressing residential exposure from the use of a top spot pet care product containing cyphenothrin. The analytical phase was conducted by Golden Pacific

Laboratories, the field phase was performed by RTI International and the clinical phase (creatinine analysis) was conducted by Lab Corp on behalf of Sergeant Pet Care Products, Inc.

SUMMARY OF STUDY RESULTS:

This study was designed to measure the systemic exposure of adults and young children (ages 3 to 6 years) based on the use of Sergeant's "top spot" pet care products containing cyphenothrin. Thirty three households successfully participated in this observational biological monitoring study (one dog, one adult and one child selected per household) which was conducted in the vicinity of Research Triangle Park, NC (location of RTI).

In this study, the application of the "top spot" products to pets was completely unscripted when performed by the participating adults. Likewise, for post application activities, all participants (adults and children) interacted with their pet as they would do so normally, in an unscripted manner. Each participant's activity diary was summarized by the investigators in order to capturing details such as whether the pet was located inside or outside; the number of minutes per day of direct contact with the pet (up to 3 hrs); and the number of petting events (0 - >11).

Although there is no cyphenothrin specific biomarker, the biomarker 3- phenoxybenzoic acid (3-PBA) was chosen by the investigators because of its extensive use as a measure of pyrethroid exposure in many exposure studies. This metabolite is also used by the Center for Disease Control (CDC) in its National Human and Nutrition Examination Survey (NHANES). In 2009, the CDC reported a median of 0.27 and a 95th percentile of 3.25 µg/L of 3-PBA for adults. It is likely that these CDC measures represent background levels and are not indicative of recent pyrethroid use.

Three-PBA is a non-pyrethroid specific metabolite that can be formed following exposure to pyrethroids such as cypermethrin, deltamethrin, esfenvalerate, phenothrin and *cis*- and *trans* – permethrin. For all estimates of dose, the *a priori* assumption is that cyphenothrin equals cypermethrin. In the following two tables, summary statistics of dose calculated by the study authors for adult and children participants are presented.

Table 1: Adult exposure, estimated by the study authors (µg/kg BW/day), for the first seven days after application.

Statistic	Mean Daily Exposure		Maximum Daily Exposure	
	Value	95th Confidence interval	Value	95th Confidence interval
Empirical				
Arithmetic Mean	0.60	0.32 – 1.01	1.91	0.87 – 3.74
95th Percentile	1.51	0.59 – 3.31	2.90	0.95 – 7.22
Lognormal				
Geometric Mean	0.29	0.2 – 0.52	0.71	0.54 – 1.60
95th Percentile	2.09	0.90 – 3.48	7.20	2.33 – 13.63

Table 2: Childrens' exposure, estimated by the study authors (µg/kg BW/day), for the first seven days after application.

Statistic	Mean Daily Exposure		Maximum Daily Exposure	
	Value	95th Confidence interval	Value	95th Confidence interval
Empirical				

Statistic	Mean Daily Exposure		Maximum Daily Exposure	
	Value	95th Confidence interval	Value	95th Confidence interval
Arithmetic Mean	3.83	2.02 – 5.95	8.76	4.96 – 13.28
95th Percentile	18.25	7.59 – 37.17	41.53	18.18 – 81.84
Lognormal				
Geometric Mean	2.08	1.01 – 3.70	5.03	2.83 – 8.38
95th Percentile	12.77	6.76 – 18.56	28.47	15.00 – 41.03

CONCLUSIONS:
This is a well conducted study and there are no critical issues regarding its execution and/or acceptability. There were issues with the interpretation of the results. That is, estimation of systemic dose based on excretion of the urinary metabolite 3-PBA. However, Versar, at the direction of Registration Action Branch II, estimated the doses in the most conservative manner resulting in estimates approximately five times higher than proposed by the registrant.

In this study, the urinary metabolite 3-PBA was measured in first morning urine voids collected from each participant for up to ten days (including 3 pre-application samples). Relying on morning voids is a common practice used in observational studies. Measures of 3-PBA collected prior to the application of Sergeant's products were subtracted from estimates of dose based on post application measures of 3-PBA. Because only morning voids were collected - instead of all urinary output per day - daily excretion of 3-PBA measured in the morning void was adjusted for daily excretion of creatinine using standard values. To convert 3-PBA to cyphenothrin, background corrected values were adjusted for the molecular weight differences (MW 214 and 375 respectively). On these two matters, there is no difference between the methods used by the study authors and the Versar review attached to this memorandum.

There are several literature studies describing the metabolism of the phenoxybenzyl moiety of pyrethroids. In Table 3, three studies used by the study authors and Versar are presented. The values selected by the study authors and Versar are also shown. The values represent the free acid and glucuronide conjugate. They do not include the glycine conjugate.

Table 3: Mammalian Metabolites, 3-PBA

Pyrethroid (species)	Reference	% of Dose as 3-PBA*	Value used by study authors	Values used by Versar
Cyphenothrin (rat)	Kaneko et al. 1994	10 – 14	12%	10%
Cypermethrin (rat)	Crawford et al. 1981	3 – 7	5%	7%
Cypermethrin (human)	Woollen et al. 1992	13±7	13%	6%

To determine the percent excreted, the study authors used average values and multiplied 12% times (13% ÷ 5%) equaling 31 percent excreted. Versar used the most conservative values and multiplied 10% times (6%/7%) equaling 8.6% excreted; about a 3.6x difference. Versar also corrected the excretion using a 70% oral absorption factor based on a rat metabolism study (Cypermethrin MRID 41551102). Details regarding the calculation of dose are presented in the attached Versar review. Overall this represents approximately a five X difference. This five-fold factor was not applied to the background values. Finally, Versar corrected the values based on an average field fortification recovery of 105 percent while the study authors did not. This

has a minimal impact on the results. It is recommended that the risk assessment team consider the above factors when considering the use of these exposures in a risk assessment.

The review package also included a letter dated 03/25/2009, from Mr. Rick Tinsworth, Exponent Inc., to Ms. Nesci and Mr. Gebkin of the Agency's Registration Division. In that letter, the authors were seeking guidance on whether this study could be use as a surrogate for the active ingredient (ai) etofenprox. Due to the conservative nature of the internal dose measurements, this may be a reasonable estimate for etofenprox provided the active ingredients have similar use patterns. However, it may be advisable to consider alternative approaches (e.g., mean values) when generalizing these data for other active ingredients.

DATA EVALUATION RECORD

STUDY TYPE: Residential Application/Post Application Biological Monitoring Study; OPPTS 875.1500/2600

TEST MATERIAL: Spot-on flea and tick formulations for dogs, containing 20-40% cyphenothrin as an active ingredient, as well as 2% pyriproxyfen.

- Sergeant's Gold® Flea and Tick Squeeze-On For Dogs, and re-released as Sentry Pro XFC Flea and Tick Squeeze-On For Dogs (EPA Reg. No. 2517-80; 40% cyphenothrin and 2% pyriproxyfen)
- Sergeant's Evolve Flea and Tick Squeeze-On For Dogs, and re-released as Sentry Pro XFT Flea and Tick Squeeze-On For Dogs (EPA Reg. No. 2517-129; 20% cyphenothrin and 2% pyriproxyfen)

SYNONYMS: Cyphenothrin; Gokilaht; Cyclopropanecarboxylic Acid, 2,2-Dimethyl-3-(2-Methyl-1-Propenyl)-, Cyano(3-Phenoxyphenyl) Methyl Ester; α-cyano-3-phenoxybenzylchrysanthemate; CAS 39515-40-7

CITATION:

Research Director: Sami Selim, Ph.D, Selim and Associates

Title: An Observational Biomonitoring Study for Measurement of Human Exposure to Cyphenothrin During and Following Application of Sergeant's Gold® Flea & Tick Squeeze-On for Dogs

Report Date: August 29, 2011

Laboratory:
Analytical
Golden Pacific Laboratories, LLC (GPL)
4720 W. Jennifer Ave., Suite 105
Fresno, CA 93722
Field
RTI International
3040 Cornwallis Road, P.O. Box 12194
Research Triangle Park, North Carolina 27709
Clinical
Lab Corp
13112 Evening Creek Drive S
San Diego, CA 92128, CA

Identifying Codes: GPL Study Number: 080303; SERGEANT'S 080303; MGK 080303; MRID #48601301; Unpublished

SPONSORS: Sergeant's Pet Care Products, Inc.
2637 South 158th Plaza, Suite 100
Omaha, NE 68130-170

McLaughlin Gormley King Company
8810 Tenth Avenue North
Minneapolis, MN 55427

EXECUTIVE SUMMARY:

This study was designed to determine the systemic exposure of adults and young children to the active ingredient cyphenothrin following application to their household dog of one of several Sergeant's or Sentry Pro Flea and Tick Squeeze-On products containing 40% or 20% cyphenothrin. This study was conducted as an observational study in 2010. Study subjects treated and interacted with their dog in their normal fashion. Urine biomonitoring was used to estimate exposure to cyphenothrin.

Thirty-three households, located within approximately one hour of Research Triangle Park, NC, were monitored. Each household provided one participating adult applicator and one participating child between the age of 3 and 6 years old who was toilet trained. Additionally, each household had only one dog. Thirty-one of the households applied a 40% ai product and two of the households applied a 20% ai product. For both products the application rate is dependent on the size of the dog. The application volume is the same for both products, thus the application rate is twice as high for the 40% ai product than the 20% ai product. The applicator had complete control over when and how to apply the product, therefore, the product may not have been applied according to labelled directions. A portion of the first morning urine void was collected from participants on each of approximately ten monitoring days, including two days prior to anticipated application, on the actual day of application (prior to application), and each of seven days following the actual application.

The urine samples were stored in a refrigerator at the participating household until picked up by study personnel. Samples were stored frozen at the field laboratory (RTI International) and the analytical laboratory. Field fortification samples were prepared at the field laboratory and sent along with every shipment of subject urine samples to the analytical laboratory. Overall field fortification recovery was 105%.

Urine samples were analyzed for the metabolite 3-phenoxybenzoic acid (3-PBA), a biomarker of cyphenothrin, using HPLC/MS/MS Method GPL-MTH-071, with a limit of quantitation (LOQ) of 1 ng/mL. All samples were also analyzed for creatinine. Creatinine values were used to normalize the 3-PBA residues determined in the random urine samples in order to estimate daily urinary 3-PBA levels.

Versar calculated daily absorbed cyphenothrin exposure in µg/day and absorbed dose in µg/kg/day. Versar corrected the urinary 3-PBA concentrations (ng/mL) for an average field fortification recovery of 105%. Also, creatinine levels in individual urine samples were used to extrapolate the urinary 3-PBA levels in first morning urine void samples to daily urinary 3-PBA levels (µg/day). In the Study Report, the authors assume adults creatinine excretion values of 1.0 g creatinine/day for females and 1.7 g/day for males. For children, they assume that expected creatinine excretion is age dependent and use the formula 0.8 g creatinine/day *age of child in years (i.e., 0.24, 0.32, 0.40, and 0.48 g creatinine/day for a 3, 4, 5, and 6 year old, respectively). For urinary 3-PBA concentrations reported as <LOQ, Versar used a value of ½ LOQ for calculation purposes. Versar corrected the post-treatment samples for background, by subtracting out each individuals average background level. Background was calculated as the minimum of either 1) the median of the pre-treatment samples or 2) the median of all sampling days. Residues of 3-PBA in the pre-treatment samples

varied, and were often quite high (<LOQ to 115 µg/day for children and <LOQ to 139 µg/day for adults).

To determine cyphenothrin exposure (µg/day), the daily urinary 3-PBA was converted to cyphenothrin using a molecular weight factor (MW of cyphenothrin/MW of 3-PBA; 375/214) and pharmacokinetic factors for the estimated absorbed dose of cyphenothrin excreted as 3-PBA (8.6%) and the estimated amount of absorbed cyphenothrin excreted in a day (70%). The absorbed cyphenothrin dose (µg/kg/day) was calculated by dividing the exposure (µg/day) by the individuals bodyweight (kg).

Limited pharmacokinetic data for cyphenothrin is available. Therefore, excretion of 3-PBA from humans and its relation to a cyphenothrin exposure had to be estimated using pharmacokinetic data from another pyrethroid, cypermethrin and a rat study using cyphenothrin. Factors used in the estimate of dose include: the fraction of cypothrin excreted as 3-PBA in rats (10%; Kaneko et al. 1984), along with a ratio of the fraction of 3-PBA excreted in humans to that excreted in a rat study (6%:7%) using cypermethrin studies (Woollen, et al. 1992 and Crawford et al. 1981). In order to provide the most conservative estimate of absorbed dose, Versar selected the worst-case pharmacokinetic values when a range of values was available. Also, pharmacokinetic data concerning the percentage of a cyphenothrin dose expected to be excreted in the urine in the day after application is unavailable, therefore, Versar used 70% as a surrogate factor from a rat metabolism study involving cypermethrin (MRID 41551102).

Daily cyphenothrin doses, as calculated by Versar, ranged from 0 to 271 µg/kg/day in children and from 0 to 139 µg/kg/day in adults. Doses were assigned a value of zero when negative values resulted from background levels that were higher than the post-treatment levels. For children, average doses increased slightly from 14.6 µg/kg/day on Day 1 to 26.9 µg/kg/day on Day 3, followed by an overall decline to 17.4 µg/kg/day on Day 7. These average values include 3 of 33 children who had urinary 3-PBA levels <LOQ for all or all but one post-treatment sample collection day. For adults, average doses remained relatively constant, except for a peak on Day 2. Average doses were 1.74 µg/kg/day on Day 1, 6.17 µg/kg/day on Day 2, and 1.91 µg/kg/day on Day 7. The average value on Day 2 was influenced by extremely high residue in the sample from HH #22. These average values also include 4 of 33 adults who had urinary 3-PBA levels <LOQ for all or all but one post treatment sample collection days. One of the adults who had urinary 3-PBA levels <LOQ for all days also had creatinine levels averaging <30 mg/dL.

Cyphenothrin doses calculated by the Registrant differed from those calculated by Versar because the Registrant did not correct for field fortification recovery, used average pharmacokinetic values instead of the most conservative values to calculate the estimated absorbed dose of cyphenothrin excreted as 3-PBA, and did not include a factor for the estimated amount of cyphenothrin excreted in a day (70%). Doses calculated by Versar were approximately 5 times higher than the doses calculated by the Registrant.

This study most of the Series 875.1500 and 875.2600 Guidelines. There are major issues of concern including:

- In humans, daily urine output and urinary concentration is variable. Only first morning void samples were collected. Ideally, a biomonitoring study will collect 24 hour urine samples to

approximate daily excretion. The residues in the urine samples were extrapolated to daily amounts using a creatinine adjustment factor. Due to uncertainties involved in an observational study as well as in human metabolism, collection of random urine samples is problematic.

- At this time, there is little pharmacokinetic data available for cyphenothrin, no human studies and limited animal study data. In order to estimate the absorbed dose of cyphenothrin, Versar and the Study Authors have used surrogate pharmacokinetic data from another pyrethroid, cypermethrin. The estimated excretion of 3-PBA from humans was estimated using data from a cyphenothrin rat study and applying a ratio of the excretion of cypermethrin (as 3-PBA) from humans to the excretion in rats. Cypermethrin data was also used as surrogate data for the estimated percentage of a cyphenothrin dose excreted in one day.

- The Registrant did not adjust the residues for field fortification recoveries.

- 3-PBA was detected in the majority of the pre-exposure samples collected from Day -3 to Day -1. The residues were variable between individuals and also a few participants had a wide range of pre-treatment residues. Versar adjusted the daily residues for the background levels in the same manner as the Registrant, using the minimum of either the 1) median of the three pre-treatment samples or 2) the median of all 10 samples analyzed in the study.

- The self-reported use of other pyrethroids in households number 1, 28, and 38 could possibly increase the levels of 3-PBA in the participants' urine samples.

COMPLIANCE:

Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. The study sponsor waived claims of confidentiality within the scope of FIFRA Section 10(d) (1) (A), (B), or (C). The Sponsor stated that the study was conducted under EPA Good Laboratory Practice Standards (40 CFR part 160), with the following exceptions: 1) the field portion of the study (observation and urine collection) was not conducted in compliance with 40CFR part 160, 2) the exposure/risk assessment was not conducted in accordance with 40CFR part 160, 3) Lab Corp, which operates under Clinical Laboratory Accreditation, analyzed urine samples for creatinine, 4) the test materials were commercial products and were not characterized according to GLP, and 5) data collection procedures for the control urine were not GLP.

CONCURRENT DISLODGEABLE RESIDUE DISSIPATION STUDY: No

GUIDELINE OR PROTOCOL FOLLOWED:
The Registrant followed Amendment 1 of GPL Study Protocol 080303, dated 9/10/2009. Early versions of the protocol were reviewed by the Independent Investigational Review Board, Inc. The final protocol was reviewed by RTIs own Internal Review Board. OPPTS Series 875, Occupational and Residential Exposure Test Guidelines, Group A: 875.1500 and Group B: 875.2600 were followed for the compliance review of this study. A compliance checklist is provided in Appendix A.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:

Information on the test materials and reference substances is provided in Tables 1 and 2, respectively.

Table 1. Test Product Information

Test Product Name	EPA Reg. No.	Formulation	Nominal % ai	Lot/Batch No.	Certificate of Analysis
Sergeant's Gold Flea & Tick Squeeze-On For Dogs (or 'Sergeant's Gold') and Sentry Pro XFC Flea and Tick Squeeze-On For Dogs (or 'Sentry Pro XFC')	2517-80	Spot-on	40.0% Cyphenothrin (CAS 39515-40-7) and 2.0% Pyriproxyfen	Not provided	Not provided
Sergeant's Evolve Flea and Tick Squeeze-On For Dogs (or 'Sereant's Evolve') and Sentry Pro XFT Flea and Tick Squeeze-On For Dogs (or 'Sentry Pro XFT')	2517-129	Spot-on	20.0% Cyphenothrin (CAS 39515-40-7) and 2.0% Pyriproxyfen	Not provided	Not provided

Table 2. Reference Substance Information

Name	Lot No.	Batch	Purity	Date Recieved	Expiration Date	Notes
3-Phenoxybenzoic acid (3-PBA) CAS 3739-38-6	07121EY	AC-448	99%	6/26/08	NA	Batch AC-448 was only used to make a stock solution which was used to fortify field QC samples. A new batch was ordered from Sigma Aldrich after it was found out that if no expiration date is given, only one year of use is supported. The new batch of standard was the same lot as the old. Analysis of the solutions showed no sign of degradation in AC-448 with respect to A-514.
	07121EY	AC-514	99%	2/10/10	2/11/11	

2. Relevance of Test Material to Proposed Formulation(s):

The test product used for this study has the same product name and formulation that appear on the test product label.

B. STUDY DESIGN:

The following amendments were made to the protocol: (1) Amendment 1 involved changes made to the protocol by RTI's IRB. Prior to the experimental start date, the entire protocol was superseded by Amendment 1; (2) Field fortification samples were prepared on each day that samples were shipped, rather than each day that samples were collected in the field; (3) Typos were corrected and the GLP-certified clinical laboratory was specified; (4) Storage stability of the biomarker was determined at 0 and 180 days to be 10 ppb, instead of up to 690 days at 40 ppb; and (5) The address of the study director changed.

The following deviations from the protocol were made: (1) Data from Household 12 and 23 were eliminated because they did not apply an approved product; (2) A modified extraction method was used for sample GPL303-018-35-D10-RI due to low sample volume; (3) The final urine sample was not collected from Household 37; (4) Lab and field QC sample recoveries were calculated by subtracting background residues in the control urine, despite resides being less than 30% of the LOQ.

1. Scenario:

The observational study was designed to determine systemic exposure of adults and young children to the active ingredient cyphenothrin following application of a spot-on product to their household dog. The dog was treated by the adult participant in their normal fashion and the household conducted their normal routines after application.

2. Number and type of individuals monitored and sites:

Thirty-three households, located within approximately one hour of Research Triangle Park, NC, were monitored for approximately 10 days between July 2009 and October 2010. Each household provided one participating adult applicator and one participating child between the age of 3 and 6 years old who was toilet trained. Additionally, each household had only one dog. All participants expressed a willingness to participate and an intent to apply one of the test products. All adult study subjects provided their signed informed consent using a form approved by the RTI Institutional Review Board (IRB) prior to participation in the study. Parental permission was also given for the children enrolled in the study. Household demographic data (age, weight, sex, height, and health of the participants) is provided in Attachment E of the Field Study Report.

The study included 31 female adults, 2 male adults, 15 female children, and 18 male children. Adults ranged in age from 26 to 46 years (average of 34.1 years). The mean age for children was 4.5 years. All participants were reported to be in excellent or good health.

Dogs
The types of dogs treated included breeds with long hair (n=4, 12.1%), medium hair (n=7, 21.2%), and short hair (n=22; 66.7%), and ranged in age from five months to 12.5 years (average of 6 years). The weight of the dogs ranged from 7.5 to 96 lbs (average of 40 lbs), with fairly even distribution across weight classes defined by the product labels: 27.3% weighed greater than 60 lbs (n=9), 27.3% weighed 40 to 60 lbs (n=9), 15.2% weighed 21 to 39 lbs (n=5), and 30.3% weighed less than 20 lbs (n=10). Most of the dogs had been treated with a flea and tick product for most of their lives on an as needed basis (n=8, 24.2%), once a month (n=21, 63.6%), or every 8 weeks (n=4, 21.1%). Some of the dogs were professionally groomed, while others were not.

3. Application Rates and Regimes:

The participating households had complete control over when and how to purchase and apply the Sergeant's brand product. As a result, there was no guarantee that the product was applied according to labeled directions, prior to its expiration date, or during the Target Monitoring Period.

Each participant recorded the product name, total time of application, if entire contents of tube were used, and method of application. Most households who completed the study (31 of 33) reported

using one of the 40% ai products (Sergeant's Gold or Sentry Pro XFC). The two remaining households (HH # 37 and #40) reported using the 20% ai product (Sentry Pro XFT).

Application Rate(s): Application rates are dependent on the size of the dog. According to the product labels, the volume of the product to be applied is the same for both Sergeant's Gold (40% ai) and Sergeant's Evolve (20% ai), thus the application rate of the 40% ai product is twice as high as the 20% ai product. The study report and labels did not provide the lb ai/gal of the products, thus Versar could not calculate the application rate in terms of lb ai/kg dog or lb ai handled.

The application rate in terms of volume applied for both products is provided below.

- 9-20 lb dog: 1.5 mL
- 21-39 lbs: 3 mL
- 40-60 lb: 4.5 mL
- Over 61 lbs: 6 mL (category only specified on the Sergeant's Gold, 40% ai label)

All participants reported using the entire contents of the tube.

Application Regime: Each household applied the product once during the monitoring period.

Application Equipment and Method: According to the product labels, the product is opened by holding the tube with the top end pointing up and away from the face and body, and then snapping or cutting off the top end. The tube is the inverted over the dog and the open end is used to part the dog's hair. The tube is squeezed firmly to apply the product (entire tube) to the dog's skin, from the back of the neck to a point midway between the neck and tail.

Most households (n=17) reported an application time of up to 1 minute. Other reported application times included 1-2 minutes (n=11), 3 minutes (n=1), 5 minutes (n=3), and 8 minutes (n=1). No explanation was provided for the long application duration of 8 minutes, which was for a household with a 25 lb cocker spaniel.

The majority of people washed their hands after use. One person also held their breath during use and changed their clothes after use.

Spray Volume: Not applicable

Equipment Calibration Procedures: Not applicable

Other Pesticide Treatments: Several households reported that they applied the test product to sites for which the product is not labelled, included to themselves, living room, and kitchen. However, the study authors believe that the participants likely misunderstood the concept of a treatment site and reported the room in which they treated their dog, or they may have gotten some of the product on themselves during treatment.

There were five homes that treated an area inside their home with another pesticide in addition to treating their dog.

- Household #1 was professionally treated three days before treatment of the dog with three products containing cyfluthrin and bifenthrin.
- Household #14 reported using an insecticide for ants, containing the active ingredients rosemary oil and cinnamon oil.
- Household #22 reported treating a participating child with insect repellant containing soybean oil and geranium oil.
- Household #28 reported treating the interior of their home with a flea spray containing the active ingredients pyriproxifen, tetramethrin, and phenothrin immediately after treating the dog.
- Household #37 reported treating their doorway and baseboards of their house with a product to control ants, containing the active ingredient bifenthrin the day after treating the dog.

4. <u>Engineering Controls</u>:

The applicators did not report using any engineering controls during application, such as gloves, eye protection, head gear, or respiratory protection.

5. <u>Time Interval(s) for Re-entry</u>: Not Applicable. The participants conducted their normal routine after application of the product.

6. <u>Replicates</u>:

Households were required to provide a product use and time activity diary during the time period of their participation. In the case of young children, a parent or other designated adult in the household assisted with urine sample collection and recording of information in the daily diary. Participating households reported activity data for the adult applicator and participating child for as few as 2 days and as many as 12 days before the day of treatment of the dog, for the day of treatment itself, and for 6 to 7 days after the day of treatment. No significant difference before and after the day of treatment

was detectable in the reported patterns of contact with the dogs by either the adult or child participants.

According to the study report, more than 180 minutes of contact with the dog was reported on 94 days for adults, about four times as often as for children (23 days). Seven households reported 69 of the 94 instances for adults, and one child accounted for 10 of the instances for children; this pattern is thought to indicate that the dog slept in the same bed as the participant, and this was more common for adults. If these reports are included in the comparison, participating adults had somewhat more dog contact than the children; omitting these reports, the children had somewhat more contact with their dogs than did the adults.

The study also reports that both adults and children typically spent several hours a day outside the home. Over all the days for which activity was reported, children were reported away from home from 0 to 17 hours, averaging 5.2 hours away from home every day. Adults also reported being away from home from 0 to 17 hours. Adults averaged 5.6 hours away from home each day.

Most of the dogs were inside dogs during the day (90%) and also at night (97%).

7. Exposure monitoring methodology:

First morning urine samples were collected each day during the study. If the first morning void was missed, a collection later in the day was allowable, as long as the necessary time information was collected.

Each household was monitored for at least 10 days both before and after application of the spot-on treatment to their dog, including two days prior to anticipated application, on the actual day of application (prior to application), and each of seven days following actual application. A few exceptions included:

- Household #26 which collected background samples 29, 30, and 31 days after application instead of prior to application.
- Household #37 which did not provide samples on Day 10 (7 days after application).
- There was insufficient urine volume for child in household #38 on Day 10 (7 days after application).

The participants were provided with mini refrigerators outfitted with a temperature logging device. They stored their urine samples inside this refrigerator until they were picked up by the RTI Study Team. Every couple of days the RTI team visited the homes to pick up samples and completed diaries at times that were convenient to the participants. The diaries were reviewed for completeness at these visits. If there were any questions about the diaries, they were resolved at that time.

The urine samples were transported by RTI in a cooler with cold packs to the RTI facility. Caps on the samples were double checked to make sure they were secured properly before they were stored in a freezer. Samples remained in the freezer until requested by GPL for shipment. The urine samples were then shipped to GPL on dry ice via overnight courier in 5 batches between 2/8/2010 and 10/26/2010.

8. Analytical Methodology:

The method used for analysis in this study allows for the quantitative determination of residues of 3-PBA in human urine. The Golden Pacific Laboratory method GPL-MTH-071, "Analytical Procedure for the Determination of 3-Phenoxybenzoic Acid (3-PBA) as a Biomarker for Cyphenothrin in Human Urine" was used to analyze the samples with some modifications.

Extraction method(s): Aliquots of human urine were acid hydrolyzed, extracted with methyltert-butyl ether (MTBE), evaporated to dryness and reconstituted in 5% acetonitrile: 95% 0.1N sodium hydroxide.

Detection method(s): The sample was submitted for HPLC/MS/MS analysis using HPLC/MS/MS for 3-PBA. A summary of the typical conditions are provided in Table 3.

Table 3. Summary of Typical HPLC/MS/MS Conditions and Mass Spectrometer Parameters

HPLC/MS/MS Conditions	
Instruments	A Sciex API4000 LC/MS/MS system was used. The HPLC consists of two Shimadzu LC-20AD HPLC Pumps, a Shimadzu SCL-10A VP Controller, and a Shimadzu SIL-20AC HT Autosampler
HPLC Column	Phenomenex Luna 3µ CI8 100A (30 mm x 2.00 mm)
Column Temperature	Ambient
Mobile Phase	A = 100% Acetonitrile and B = Optima Water (pH adjusted to 7 with ammonium hydroxide) Time A% B% 0.0 00 100 3.0 40.0 60.0 4.0 40.0 60.0 4.1 0.0 100 6.0 0.0 100
Flow Rate	0.500 mL/minute
Injector	Autosampler
Injection Volume:	10 µL
Retention Time:	3-PBA ~1.70 minutes
Mass Spectrometer Parameters	
Interface	Turbo-Ion Spray (ESI)
Polarity	Negative
Scan Type	MRM Monitoring with Unit resolution
Ions Monitored	(Ql) m/z 212.77 (Q3) m/z 93.3

Method validation: The method was validated prior to the start of the study in GPL Study No. 080310, however, the results were not provided.

The limit of quantitation (LOQ) for 3-PBA in human urine was 1.00 ng/mL.

Instrument performance and calibration: Calibration standards were injected every three to five sample injections as well as at the beginning and

ending of the injection sequence. At least six different standard concentrations were injected within each analytical set. A standard curve was generated. The correlation coefficients were all greater than 0.99

Quantification: The concentration (ng/mL) of 3-PBA detected in sample extracts was interpolated from the standard calibration curve. The linear regression function was used to calculate a best-fit line and to determine concentration of the analyte found during sample analysis.

9. Quality Control:

Lab Recovery: Typically, each set consisted of an untreated control, two laboratory fortification samples, field study samples and field fortification samples. Laboratory fortifications were prepared by directly fortifying untreated control samples (collected from laboratory personnel) at the nominal level of 1.00 ng/mL (LOQ), 100 ng/mL, and 500 ng/mL. The residues found in control samples were <LOQ. However, they were subtracted from the laboratory fortification residues as a correction for background in lab QC samples. As shown in Table 4, the overall average laboratory recovery was 108%.

Table 4. Summary of Laboratory Recoveries

Fortification Level (ng/mL)	n	Minimum	Maximum	Average	Standard Deviation
1	54	92.3	125	111	7.4
100	39	84	117	104	6.1
500	15	97.4	114	108	4.5
Overall	108	84	125	108	7.4

Field recovery: Field fortification samples were sent along with every shipment of subject urine samples to the analytical laboratory. Each shipment included three low level (10 to11.4 ng/mL) and three high level (100 to 112 ng/mL) field fortification samples. The field fortification solutions of the biomarker, diluted in water, were prepared and pre-measured by GPL. The vials containing these field fortification solutions along with separate control urine samples were then shipped to RTI. RTI prepared the field fortification samples. Control urine samples were kept frozen until their use at RTI. After the samples were spiked, they were then exposed to ambient conditions (i.e., weathered) for not more than 48 hours at room temperature in a location away from possible contamination. After 48 hours, the field fortified samples were placed into a freezer until shipment. Packaging, storage and shipment of the field fortification samples were the same as for the study samples.

As shown in Table 5, the overall average field fortification recovery was 105%. The recoveries were corrected for residues found in control samples, which were <LOQ.

Table 5. Summary of Field Fortification Recoveries

Fortification Level (ng/mL)	n	Minimum	Maximum	Average	Standard Deviation
10-11.4	52	92	122	106	5.7
100-113	52	91	119	103	6.1
Overall	104	91	122	105	6.1

Formulation: Spot-on formulation containing 40% cyphenothrin (Sergeant's Gold or Sentry Pro XFC) or 20% cyphenothrin (Sergeant's Evolve or Sentry Pro XFT). Certificates of analysis were not provided.

Tank mix: Not applicable

Travel Recovery: Travel recovery samples were prepared, however the samples were not analyzed.

Storage Stability: A storage stability study of 3-PBA was conducted to evaluate its stability in urine when stored at room temperature and refrigerated temperature for 7 days and stored at frozen temperature for 3 months (GPL Study No. 080311). The results were not provided. In the current study, a six month freezer storage stability sample was also generated and analyzed to cover the longer storage conditions. At 6 months, the corrected average recovery (n = 3) of 3-PBA in urine was 108%.

II. RESULTS AND CALCULATIONS

Versar calculated daily absorbed cyphenothrin exposure in µg/day and dose in µg/kg/day using the measured 3-PBA concentrations in the first morning urine voids adjusted for 1) creatinine levels, 2) field fortification recovery, 3) background levels, 4) pharmacokinetic factors, and 5) molecular weight factors. These adjustments are discussed below.

Creatinine Correction:The creatinine levels found in the individual urine samples were used to extrapolate the urinary 3-PBA levels in the first morning void urine samples to daily urinary 3-PBA levels (µg/day). In the Study Report, the authors assume that for adults the expected creatinine excretion is 1.0 g creatinine/day for females and 1.7 g/day for males. For children, they assume that expected creatinine excretion is age dependent and use the assumption of 0.8 g creatinine/day *age of child in years (i.e., 0.24, 0.32, 0.40, and 0.48 g creatinine/day for a 3, 4, 5, and 6 year old, respectively).

Field Fortification Correction: Versar corrected the urinary 3-PBA concentrations (ng/mL) for an average field fortification recovery of 105%. For urinary 3-PBA concentrations reported as <LOQ, Versar used a value of ½ LOQ for calculation purposes.

Background Correction: Versar corrected the post-treatment samples for background, by subtracting out each individuals average background level. Background was calculated as the minimum of either 1) the median of the pre-treatment samples or 2) the median of all sampling days. Residues of 3-PBA in the pre-treatment samples varied, and were often quite high (<LOQ to 115 µg/day for children and <LOQ to 139 µg/day for adults).

Molecular Weight Factor: The daily urinary 3-PBA was converted to cyphenothrin using a molecular weight factor (MW of cyphenothrin/MW of 3-PBA; 375/214).

Pharmacokinetic Factors: At this time, there are no human pharmacokinetic data available for cyphenothrin, and limited rat study data. In order to estimate the absorbed dose of cyphenothrin, Versar and the Study Authors have used surrogate pharmacokinetic data from another pyrethroid, cypermethrin. Both are type II pyrethroids, cypermethrin has 2 chlorines on the acid portion of the molecule, so the metabolism of the two molecules is probably similar. The urinary excretion of 3-PBA in humans following cyphenothrin exposure was estimated using the fraction of cyphenothrin excreted as 3-PBA in rats (10%; Kaneko et al. 1984), multiplied by the ratio of 3-PBA excreted in humans to that same excretion in rats (6%/7%) following exposure to cypermethrin (Woollen, et al. 1992 and Crawford et al. 1981). Versar also factored in cypermethrin excretion data from a rat metabolism study which determined that greater than 70% of the cypermethrin is excreted in 24 hours, with 85-97% within 72 hours (MRID 41551102). Versar selected the worst-case pharmacokinetic values when a range of values was available. A summary of the pharmacokinetic data used to estimate absorbed cyphenothrin dose is provided in Table 6.

Table 6. Pharmacokinetic Values Used in Calculation of Cyphenothrin Absorbed Dose

Factor	Reported Range	Used by Registrant	Used By Versar
Percentage of **cyphenothrin** (oral dose) excreted as 3-PBA in rats [Kaneko et al. 1984] *Input #1*	10-14%	12%	10%
Percentage of **cypermethrin** (oral dose) excreted as 3-PBA in humans [Woollen, et al. 1992] *Input #2*	13±7%	13%	6%
Percentage of **cypermethrin** (oral dose) excreted as 3-PBA in rats [Crawford et al. 1981] *Input #3*	3-7%	5%	7%
Percentage of cyphenothrin excreted as 3-PBA in humans estimated using the three inputs above.	NA	31% [12%*(13%/5%)]	8.6% [10%*(6%/7%)]
Percentage of **cypermethrin** excreted in urine from a rat metabolism study following radio labeled dosing [MRID 41551102]	>70% excreted in 24 hours, with 85-97% excreted within 72 hours.	Not factored in	70%

An equation for the calculation of absorbed daily dose is provided as Equation 1 below.

$$\textbf{ADD (µg/kg/day)} = \frac{\textbf{3-PBA (µg/day) * (MWF)}}{\textbf{F1 * F2 * BW (kg)}} \qquad \textbf{Eq. 1}$$

Where:

ADD (µg/kg/day) = Absorbed daily dose of the active ingredient (µg/kg/day)
3-PBA (µg/day) = Metabolite recovered per day, corrected for field fortification recovery and background level and adjusted for creatinine level
MWF = Molecular weight factor – the ratio of the molecular weight of cyphenothrin (375) to the molecular weight of 3-PBA (214)
F1 = The percentage of cyphenothrin excreted as 3-PBA (8.6%) This number is calculated as:
10% (fraction of cyphenothrin excreted as 3-PBA in rats) * 6%/7% (ratio of fraction of cypermethrin excreted as 3-PBA in humans over fraction of cypermethrin excreted as 3-PBA in rats.
F2 = The estimated percentage of cyphenothrin that will be excreted in a day (70%) based on surrogate value from cypermethrin study data.
BW (kg) = Body weight of individual

Urinary 3-PBA levels and absorbed cyphenothrin dose estimates are provided in Table 7 for children and Table 10 for adults. The absorbed doses are summarized by participant in Tables 8 for children and 11 for adults. Additionally, Tables 9 and 12 summarize the doses by day for children and adults, respectively.

As shown in Tables 8 and 11, daily absorbed cyphenothrin doses, as calculated by Versar, ranged from 0 to 271 µg/kg/day in children and from 0 to 139 in adults. Doses were assigned a value of zero when negative values resulted from background levels that were higher than the post-treatment levels. As shown in Table 9 and graphically presented in Figure 1, average absorbed doses for children increased slightly from 14.6 µg/kg/day on Day 1 to 26.9 µg/kg/day on Day 3, followed by an overall decline to 12.0 µg/kg/day on Day 8. These average values include 3 of 33 children who had urinary 3-PBA levels <LOQ for all or all but one post treatment sample collection days. As shown in Table 12 and graphically presented in Figure 2, average absorbed doses for adults remained relatively constant, except for a peak on Day 2. Average doses were 1.74 µg/kg/day on Day 1, 6.17 µg/kg/day on Day 2, and 1.91 µg/kg/day on Day 7. The average value on Day 2 was influenced by high residues in the sample from HH #22. These average values include 3 of 33 adults who had urinary 3-PBA levels <LOQ for all or all but one post treatment sample collection days.

Cypermethrin doses calculated by the Registrant differed from those calculated by Versar because the Registrant did not correct for field fortification recovery, used average pharmacokinetic values instead of the most conservative values to calculate the estimated absorbed dose of cyphenothrin excreted as 3-PBA (see Table 6), and did not include a factor to account for the estimate that only approximately 70% of a cyphenothrin dose would be excreted in the first day after exposure or treatment. Doses calculated by Versar were approximately 5 times higher than the doses calculated by the Registrant.

III. DISCUSSION:

This study met most of the Series 875.1500 and 875.2600 Guidelines. There are major issues of concern which include:

- In humans, daily urine output and urinary concentration is variable. Only first morning void samples were collected. Ideally, a biomonitoring study will collect 24 hour urine samples to approximate daily excretion. The residues in the urine samples were extrapolated to daily amounts using a creatinine adjustment factor. Due to uncertainties involved in an observational study as well as in human metabolism, collection of random urine samples is problematic.

- At this time, there is little pharmacokinetic data available for cyphenothrin, no human studies and limited animal study data. In order to estimate the absorbed dose of cyphenothrin, Versar and the Study Authors have used surrogate pharmacokinetic data from another pyrethroid, cypermethrin. The estimated excretion of 3-PBA from humans was estimated using data from a cyphenothrin rat study and applying a ratio of the excretion of cypermethrin (as 3-PBA) from humans to the excretion in rats. Cypermethrin data was also used as surrogate data for the estimated percentage of a cyphenothrin dose excreted in one day.

- The Registrant did not adjust the residues for field fortification recoveries.

- 3-PBA was detected in the majority of the pre-exposure samples collected from Day -3 to Day -1. The residues were variable between individuals and also a few participants had a wide range of pre-treatment residues. Versar adjusted the daily residues for the background levels in the same manner as the Registrant, using the minimum of either the 1) median of the three pre-treatment samples or 2) the median of all 10 samples analyzed in the study.

- The self-reported use of other pyrethroids in households number 1, 28, and 38 could possibly increase the levels of 3-PBA in the participants' urine samples.

Table 7. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Children							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine corrections (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
HH#2 Age 4 24.09 kg	-3	3.08	68.9	1.36	1.02	--	--
	-2	3.45	107.1	0.982		--	--
	-1	3.35	99.9	1.02		--	--
	1	2.78	60	1.41		11.4	0.473
	2	5.99	98.1	1.86		24.5	1.02
	3	4.69	134.4	1.06		1.21	0.050
	4	4.32	89.8	1.47		13.0	0.538
	5	5.55	106.9	1.58		16.4	0.679
	6	6.65	95.7	2.12		32.0	1.33
	7	5.67	75.2	2.30		37.3	**1.55**
HH# 1 Age 6 24.09 kg	-3	1.35	110.20	0.560	0.69	--	--
	-2	4.2	121.80	1.58		--	--
	-1	1.87	124.20	0.688		--	--
	1	10.7	61.00	8.02		214	**8.89**
	2	3.35	74.80	2.05		39.7	1.65
	3	3.78	81.70	2.12		41.7	1.73
	4	4.66	90.40	2.36		48.7	2.02
	5	3.04	78.30	1.77		31.7	1.32
	6	<1.0	23.90	1.00		9.23	0.383
	7	2.36	86.30	1.25		16.4	0.681
HH# 3 Age3 18.64 kg	-3	13.5	68.5	4.50	4.50	--	--
	-2	29.2	165.1	4.04		--	--
	-1	42.1[6]	81.7	11.78		--	--
	1	24.2	38.9	14.22		284	**15.2**
	2	33.2	62.8	12.08		221	11.9
	3	40.4	83.1	11.11		193	10.4
	4	20.3	92.6	5.01		14.8	0.793
	5	62.4	163.8	8.71		123	6.59
	6	39.8	114.9	7.92		100	5.35
	7	9.83	32	7.02		73.5	3.94
HH# 4 Age 3 15.91 kg	-3	4.61	94	1.12	0.49	--	--
	-2	<1.0	54.3	0.221		--	--
	-1	1.95	90.8	0.491		--	--
	1	20.2	60.7	7.61		208	13.1
	2	12.6	87.2	3.30		82.1	5.16
	3	15.4	82.3	4.28		111	6.95
	4	31.5	71.9	10.01		278	**17.5**
	5	37.3	120.9	7.05		192	12.0
	6	56.1	161.6	7.93		217	13.7
	7	12.5	42.8	6.68		181	11.4
HH#6 Age 5 17.73 kg	-3	<LOQ	30.2	0.662	1.15	--	--
	-2	2.05	50.1	1.56		--	--
	-1	2.21	73.1	1.15		--	--
	1	14.9	65.1	8.72		221	12.5
	2	26.2	114.7	8.70		221	12.4
	3	13.6	86.9	5.96		140	7.92
	4	8.39	47.3	6.76		164	9.23
	5	31.7	109.7	11.01		288	**16.2**
	6	8.43	89.2	3.60		71.5	4.03
	7	6.12	50.3	4.64		102	5.74
HH# 7	-3	2.19	67.1	1.49	1.49	--	--

Table 7. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Children							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine corrections (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
Age 6 27.27 kg	-2	2.16	57.1	1.73		--	--
	-1	1.89	73	1.18		--	--
	1	<LOQ	28.8	0.833		-19.2	0
	2	5	67.9	3.37		54.7	2.01
	3	2.89	101.4	1.30		-5.52	0.00
	4	8.63	77.3	5.10		105	**3.87**
	5	6.3	91.4	3.15		48.5	1.78
	6	1.31	17.6	3.40		55.8	2.05
	7	1.83	27.4	3.05		45.6	1.67
HH #8 Age 5 23.64 kg	-3	Not Sampled			0.27	--	--
	-2	<LOQ	70.5	0.284		--	--
	-1	<LOQ	75.7	0.264		--	--
	1	<LOQ	81.2	0.246		-0.807	0
	2	<LOQ	102.8	0.195		-2.32	0
	3	13.8[6]	71	7.40		208	8.81
	4	12.2	113.4	4.10		112	4.72
	5	145	127.5	43.3		1257	**53.2**
	6	27.7	123.3	8.56		242	10.2
	7	22.5	90.2	9.50		270	11.4
	8	13.8	60.9	8.55		242	10.2
HH #9 Age 6 20.91 kg	-3	<LOQ	58	0.41	0.41	--	--
	-2	<LOQ	92.7	0.26		--	--
	-1	8.38[6]	97.5	3.93		--	--
	1	35.6	65.1	25.0		718	34.3
	2	23.3	86.3	12.3		348	16.7
	3	95.3	139.5	31.2		900	43.0
	4	7.89	50	7.21		199	9.50
	5	19.9	153.6	5.92		161	7.69
	6	32.9	179.8	8.36		232	11.1
	7	104	124.1	38.3		1107	**52.9**
HH #10 Age 5 15.91 kg	-3	2.34	149.8	0.595	0.89	--	--
	-2	1.83	69.6	1.00		--	--
	-1	1.59	68	0.891		--	--
	1	2.52	141.3	0.679		-6.17	0
	2	8.21	80.8	3.87		87.0	5.47
	3	6.99	24.7	10.8		289	18.2
	4	21.4	90.3	9.03		238	14.9
	5	20.1	118.3	6.47		163	10.2
	6	45.8	118.6	14.7		404	**25.4**
	7	22.1	85.3	9.87		262	16.5
HH #11 Age 3 12.93 kg	-3	<LOQ	50.8	0.236	0.49	--	--
	-2	2.08	97.1	0.490		--	--
	-1	1.67	59.2	0.645		--	--
	1	82.9	70.1	27.0		775	**60.9**
	2	27.8	117.2	5.42		144	11.3
	3	13.9	165.6	1.92		41.7	3.28
	4	7.7	46.3	3.80		96.7	7.60
	5	12.5	69.7	4.10		105	8.28
	6	9.42	30.4	7.08		193	15.1
	7	14.4	70.1	4.70		123	9.65
HH #14	-3	Not Sampled			0.89	--	--

Table 7. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Children							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine corrections (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
Age 5 20.45 kg	-2	1.23[6]	107.5	0.44		--	--
	-1	2.43[6]	68.6	1.35		--	--
	1	9.3[6]	50	7.09		181	8.84
	2	12.2	18.7	24.9		700	34.2
	3	29	85	13.0		354	17.2
	4	34.5	49.5	26.6		749	36.6
	5	66.3	89.2	28.3		801	**39.2**
	6	18.7	53.1	13.4		366	17.9
	7	27.6	58.2	18.1		502	24.5
	8	36.1	129.3	10.6		285	13.9
HH #15 Age 5 25 kg	-3	5.19	117.8	1.68	1.69	--	--
	-2	6.41	115.7	2.11		--	--
	-1	7.08	160	1.69		--	--
	1	6.13	147.4	1.58		-2.96	0
	2	13.1	149.3	3.34		48.4	1.94
	3	34.4	190.3	6.89		152	6.08
	4	19.2	61.5	11.9		298	**11.9**
	5	46.2	184.1	9.56		230	9.20
	6	21.8	82	10.1		247	9.86
	7	28.8	111.2	9.87		239	9.56
HH#16 Age 4 20.45 kg	-3	<LOQ	168.4	0.095	0.10	--	--
	-2	<LOQ	175.1	0.091		--	--
	-1	<LOQ	119.9	0.133		--	--
	1	<LOQ	220.6	0.073		-0.657	0
	2	2.18	173.3	0.383		8.42	0.412
	3	4.83	182.5	0.807		20.8	**1.02**
	4	4.38	175	0.763		19.5	0.954
	5	3.4	129.4	0.801		20.6	1.01
	6	1.96	104.6	0.571		13.9	0.680
	7	2.07	176	0.358		7.69	0.376
HH #17 age 5 18.18 kg	-3	1.25	87.4	0.545	0.57	--	--
	-2	1.86	62.4	1.14		--	--
	-1	2.18	146.7	0.566		--	--
	1	2.47	134.2	0.701		3.94	0.217
	2	3.68	153.5	0.913		10.1	0.558
	3	9.67	145.7	2.53		57.3	3.15
	4	5.23	98.5	2.02		42.5	2.34
	5	5.23	139.4	1.43		25.2	1.39
	6	5.92	78.5	2.87		67.4	**3.71**
	7	5.1	147.1	1.32		22.0	1.21
HH #18 Age 6 20.45 kg	-3	1.32	110.8	0.545	0.85	--	--
	-2	2.79	150.9	0.845		--	--
	-1	2.49	110.1	1.03		--	--
	1	11.1	137.7	3.69		82.9	4.06
	2	10.6	115.2	4.21		98.2	4.80
	3	86.9	156.5	25.4		717	**35.0**
	4	76.5	197.4	17.7		493	24.1
	5	36.6	146.4	11.4		309	15.1
	6	26.8	156.4	7.83		204	9.98
	7	14.6	88.2	7.57		196	9.60
HH #20	-3	2.44	158.6	0.469	0.47	--	--

Table 7. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Children							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine corrections (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
Age 4 18.18 kg	-2	1.14	99.3	0.350		--	--
	-1	1.1	68.7	0.488		--	--
	1	11.3	140.4	2.45		57.9	3.19
	2	33	175.2	5.74		154	**8.47**
	3	7.75	69.8	3.38		85.1	4.68
	4	14.5	146.1	3.02		74.6	4.11
	5	11.6	118.2	2.99		73.7	4.05
	6	4.96	46.5	3.25		81.2	4.47
	7	4.21	80	1.60		33.1	1.82
HH #22 Age 3 11.36 kg	-3	60.5	79.4	17.4	18.05	--	--
	-2	56.3	71.3	18.0		--	--
	-1	39.7	42.7	21.3		--	--
	1	190	49.2	88.3		2051	181
	2	7.49[6]	51.3	3.34		-430	0
	3	437	102	97.9		2333	**205**
	4	211	84.4	57.1		1142	101
	5	127	75.3	38.6		599	52.7
	6	62.6	78.8	18.2		3.20	0.282
	7	67	74.2	20.6		75.7	6.66
HH #24 Age 6 19.09 kg	-3	Not Sampled			1.29	--	--
	-2	1.02	38.7	1.20		--	--
	-1	2.08	69.6	1.37		--	--
	1	1.15	61.9	0.849		-12.7	0
	2	3.38	61.7	2.50		35.6	1.86
	3	6.28[6]	76.9	3.73		71.5	3.75
	4	4.02	45.9	4.00		79.4	4.16
	5	6.36	69.5	4.18		84.6	4.43
	6	5.71	63.7	4.10		82.1	4.30
	7	5.23	54.9	4.35		89.6	4.70
	8	4.55	47.6	4.37		90.1	**4.72**
HH #26 Age 6 21.82 kg	-3[7]	14.2	181.6	3.57	3.57	--	--
	-2[7]	18.1	147.4	5.61		--	--
	-1[7]	5.81	77.2	3.44		--	--
	1	6.27	147.7	1.94		-47.7	0
	2	97.7	117.8	37.9		1003	46.0
	3	119	82.6	65.9		1819	83.4
	4	98.9	55	82.2		2296	105
	5	74.3	73.6	46.1		1243	57.0
	6	34.2	45.8	34.1		893	40.9
	7	241	130.3	84.6		2365	**108**
HH #27 Age 6 16.82 kg	-3	212[6]	96.8	100	78.21	--	--
	-2	145[6]	57.9	114		--	--
	-1	167[6]	76.5	100		--	--
	1	127[6]	51.7	112		995	**59.2**
	2	85.5	70.8	55.2		-672	0
	3	77.6	67.5	52.6		-749	0
	4	92.4	59.6	70.9		-214	0
	5	57.5	47.8	55.0		-678	0
	6	88.2	73.9	54.6		-691	0
	7	91.7	49	85.6		214	12.7
HH #28	-3	Not Sampled			9.39	--	--

Table 7. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Children							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine corrections (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
Age 4 18.18 kg	-2	26.7	94.2	8.64		--	--
	-1	13.8	41.5	10.1		--	--
	1	31.2	100.2	9.49		3.02	0
	2	263	69.6	115		3089	170
	3	367	87	129		3481	191
	4	340	58.1	178		4935	**271**
	5	214	94.7	68.9		1737	95.6
	6	107	63.9	51.0		1216	66.9
	7	66.9	52	39.2		871	47.9
	8	46.2	73.4	19.2		286	15.7
HH #29 Age 4 22.73 kg	-3	1.53	139.7	0.33	0.33	--	--
	-2	1.63	127	0.39		--	--
	-1	<LOQ	62.2	0.26		--	--
	1	16.6	99	5.11		139	6.14
	2	301	136.9	67.0		1947	**85.7**
	3	69	52.5	40.1		1160	51.0
	4	171	103.9	50.2		1455	64.0
	5	149	123.8	36.7		1062	46.7
	6	113	90.6	38.0		1100	48.4
	7	56.3	66.5	25.8		744	32.7
HH #30 Age 5 20.45 kg	-3	1.86	87.4	0.811	0.40	--	--
	-2	<LOQ	41	0.488		--	--
	-1	<LOQ	58.7	0.341		--	--
	1	<LOQ	70.6	0.283		-3.35	0
	2	<LOQ	56.1	0.357		-1.21	0
	3	<LOQ	35.9	0.557		4.65	**0.227**
	4	<LOQ	39.2	0.510		3.28	0.160
	5	<LOQ	45.5	0.440		1.21	0.059
	6	<LOQ	72.3	0.277		-3.55	0
	7	<LOQ	83.4	0.240		-4.62	0
HH #31 Age 4 16.36 kg	-3	<LOQ	49	0.327	0.33	--	--
	-2	<LOQ	45.7	0.350		--	--
	-1	<LOQ	130.9	0.122		--	--
	1	13	42.8	9.26		261	15.9
	2	10	51.1	5.96		165	10.1
	3	30.7	56.6	16.5		473	**28.9**
	4	14.5	45	9.82		277	16.9
	5	18.5	100.5	5.61		154	9.43
	6	20.9	80.5	7.91		222	13.5
	7	13	51	7.77		217	13.3
HH #32 Age 3 17.27 kg	-3	Not Sampled			0.28	--	--
	-2	<LOQ	48.9	0.245		--	--
	-1	1.42	101.1	0.321		--	--
	1	22.6	17.1	30.2		874	50.6
	2	110	78.8	31.9		924	**53.5**
	3	52.5	59.8	20.1		578	33.5
	4	80.2	80.2	22.9		659	38.2
	5	43.8	80.7	12.4		354	20.5
	6	83.1	116.3	16.3		469	27.1
	7	9.8	16.6	13.5		386	22.3
	8	76.7	111.1	15.8		453	26.2

Table 7. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Children							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine corrections (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
HH #33 Age 4 17.73 kg	-3	<LOQ	64.5	0.248	0.26	--	--
	-2	<LOQ	55.6	0.288		--	--
	-1	<LOQ	60.6	0.264		--	--
	1	<LOQ	22.7	0.705		12.9	0.726
	2	<LOQ	18.1	0.884		18.1	1.02
	3	<LOQ	17.9	0.894		18.4	1.04
	4	<LOQ	16.6	0.964		20.4	**1.15**
	5	<LOQ	18.9	0.847		17.0	0.960
	6	<LOQ	36.6	0.437		5.06	0.285
	7	<LOQ	37	0.432		4.92	0.277
HH #34 Age 4 15.91 kg	-3	3.17	85.9	1.12	0.97	--	--
	-2	2.41	75.7	0.970		--	--
	-1	2.83	116	0.74		--	--
	1	5.53	79.5	2.12		33.6	2.11
	2	1.62	20.2	2.44		43.0	2.71
	3	1.33[6]	126.8	0.32		-19.0	0
	4	14	97	4.40		100	6.29
	5	12.9	85.7	4.59		106	**6.64**
	6	5.59	43.8	3.89		85.3	5.36
	7	13.3	98.8	4.10		91.5	5.75
HH #35 Age 3 23.18 kg	-3	Not Sampled			2.65	--	--
	-2	14.3	116	2.82		--	--
	-1	8.52	78.7	2.47		--	--
	1	15.2	145.9	2.38		-7.73	0
	2	5.69	44.4	2.93		8.27	0.357
	3	16.6	110.9	3.42		22.6	0
	4	8.15	58.7	3.17		15.4	0.665
	5	31	83.2	8.52		171	**7.40**
	6	17	107.6	3.61		28.2	1.22
	7	11.7	83.5	3.20		16.3	0.701
	8	17.6	119.4	3.37		21.1	0.911
HH #36 Age 3 11.36 kg	-3	8.6	38.8	5.07	5.07	--	--
	-2	11.9	135	2.01		--	--
	-1	22.2	93.6	5.42		--	--
	1	15.9	73.4	4.95		-3.4	0
	2	417	164.3	58.0		1546	136
	3	37.5	28.7	29.9		724	63.8
	4	59	54.1	24.9		580	51.1
	5	160	54.1	67.6		1826	**161**
	6	150	67.2	51.0		1342	118
	7	180	90.3	45.6		1183	104
HH #37 Age 5 17.27 kg	-3	<LOQ	70.7	0.283	0.28	--	--
	-2	<LOQ	78.1	0.256		--	--
	-1	1.93	79.2	0.928		--	--
	1	3.43	66.5	1.96		49.1	2.84
	2	8.18	72.3	4.31		118	6.81
	3	53.5[6]	66.5	30.6		887	**51.4**
	4	12.8	85.2	5.72		159	9.20
	5	9.1	80.4	4.31		118	6.81
	6	9.55	82.9	4.39		120	6.94
	7	Not sampled				--	--

Table 7. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Children							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine corrections (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
HH #38 Age 3 13.64 kg	-3	9.58	45.5	4.81	5.04	--	--
	-2	23.6	107.1	5.04		--	--
	-1	20.2	90.1	5.12		--	--
	1	24.8	90.3	6.28		36.2	2.66
	2	7.6	17.5	9.93		143	**10.5**
	3	2.9	14	4.73		-8.82	0
	4	6.58	22.9	6.57		44.7	3.28
	5	23	87.5	6.01		28.4	2.08
	6	19.5	68.3	6.53		43.5	3.19
	7	20.8	Not analyzed	--		--	--
HH #39 Age 5 21.82 kg	-3	<LOQ	91.6	0.218	0.57	--	--
	-2	1.65	109.8	0.572		--	--
	-1	2.12	90	0.897		--	--
	1	<LOQ	46.6	0.429		-4.18	0
	2	12.3	41.8	11.2		311	14.2
	3	7.36	58.5	4.79		123	5.65
	4	12.4	76.1	6.21		165	7.54
	5	10.2	30.4	12.8		357	16.3
	6	49.2	123	15.2		428	**19.6**
	7	24.7	73.5	12.8		357	16.4
HH #40 Age 4 18.18 kg	-3	<LOQ	31.9	0.502	0.40	--	--
	-2	<LOQ	40	0.400		--	--
	-1	<LOQ	64.2	0.249		--	--
	1	<LOQ	21.9	0.731		9.66	0.531
	2	<LOQ	38.5	0.416		0.455	0.0250
	3	<LOQ	49.5	0.323		-2.24	0
	4	<LOQ	36.3	0.441		1.19	0.0655
	5	<LOQ	76.1	0.210		-5.54	0
	6	<LOQ	35.7	0.448		1.41	0.0774
	7	1.34	23.9	1.71		38.2	**2.10**

1. First morning void urine samples were analyzed. LOQ = 1.00 ng/mL. Residues <LOQ were assigned a value of ½ LOQ for calculation purposes.
2. Urinary 3-PBA (µg/day) = [3-PBA concentration corrected for field fortification (ng/mL) / measured creatinine (mg/dL) * 1 g/1000 mg * 1 dL/100 mL] * expected creatinine (g/day) *1 µg/1000 ng. 3-PBA concentrations were corrected using an average field fortification recovery of 105%. Expected creatinine values are: 0.24 g/day for 3 yr olds, 0.32 g/day for 4 yr olds, 0.40 g/day for 5 yr olds, and 0.48 g/day for 6 yr olds.
3. Background 3-PBA (µg) = the minimum of either 1) median of the pre-treatment samples or 2) median of all sampling days.
4. Absorbed Cyphenothrin exposure (µg/day) = [urinary 3-PBA (µg) – Background urinary 3-PBA (µg)] * [MW ratio (375/214)/((fraction cypermethin excreted as 3-PBA in humans (0.06)/fraction of cypermethrin excreted as 3-PBA in rat (0.07) *fraction of cyphenothrin excreted as 3-PBA in rats (0.1))] / fraction of cypermethrin expected to be excreted in 24 hours (0.7).
5. Absorbed Cyphenothrin dose (µg/kg/day) = Cyphenothrin exposure (µg/day)/ Bodyweight (kg). Bolded values are the maximum values. Negative values were assigned a value of zero for further calculation purposes (eg, averages).
6. Average of replicate analysis.
7. Pre-treatment samples for household #26 were collected 29, 30, and 31 days after application instead of prior to application.

Table 8. Summary of Daily Absorbed Cyphenothrin Dose for Children (Post-Treatment) (µg/kg/day)				
Study Participant	Minimum	Maximum	Average	Standard Deviation
HH #2	0.050	1.55	0.805	0.522
HH #1	0.383	8.89	2.38	2.93
HH #3	0.793	15.2	7.73	4.99
HH #4	5.16	17.5	11.4	4.16
HH #6	4.03	16.2	9.72	4.26
HH #7	0	3.87	1.62	1.33
HH #8	0	53.2	11.2	17.7
HH #9	7.69	52.9	25.0	18.2
HH #10	0.0	25.4	13.0	8.45
HH #11	3.278	60.9	16.6	19.9
HH #14	8.84	39.2	25.0	11.9
HH #15	0	11.9	6.94	4.46
HH #16	0	1.02	0.635	0.389
HH #17	0.217	3.71	1.80	1.31
HH #18	4.06	24.1	11.3	7.5
HH #20	1.82	8.47	4.40	2.04
HH #22	0	205	78.0	86.7
HH #24	0	4.72	3.45	1.82
HH #26	0	108	63.0	38.8
HH #27	0	59.2	10.3	22.1
HH #28	0.166	271	95	95.8
HH #29	6.14	85.7	47.8	24.7
HH #30[1]	0.0	0.227	0.064	0.093
HH #31	9.43	28.9	15.4	6.55
HH #32	20.5	53.5	34.1	13.5
HH #33[1]	0.277	1.15	0.780	0.364
HH #34	0	6.64	4.12	2.53
HH #35	0	7.40	1.61	2.58
HH #36	0	160.8	90.6	55.4
HH #37	2.84	51.4	14.0	18.4
HH #38	0	10.5	3.61	3.57
HH #39	0	19.6	11.4	7.10
HH #40[1]	0	2.10	0.400	0.774
Overall				
Minimum	0.0	0.227	0.064	0.093
Maximum	20.5	271	101	95.8
Average	2.29	43.4	19.2	14.9
Standard Deviation	4.30	61.9	26.7	23.0

1. 3-PBA residues were <LOQ in all or all but one post-treatment urine sample.

1

Table 9. Summary of Daily Absorbed Cyphenotrhin Dose By Study Day for Children (µg/kg/day)						
Study Day	n	Minimum	Maximum	Average	Standard Deviation	Median
1	33	0.00	181	14.6	34.2	2.11
2	33	0.00	170	19.9	39.2	5.16
3	33	0.00	205	26.9	49.1	6.08
4	33	0.00	271	25.2	51.7	7.54
5	33	0.00	161	20.5	33.4	7.69
6	33	0.00	118	14.9	24.0	5.36
7	31	0.00	108	17.4	27.1	9.56
8	6	0.91	26.2	12.0	8.93	12.1

Table 10. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Adults							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine correction (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
HH # 2, Female, 129.55 kg	-3	<LOQ	72.6	0.69	0.86	--	--
	-2	1.85	179.9	0.98		--	--
	-1	2.57	284	0.86		--	--
	1	4.41	124.8	3.37		73.1	**0.564**
	2	2.42	107.9	2.14		37.2	0.287
	3	1.27	102.9	1.18		9.16	0.071
	4	3.19	144.8	2.10		36.1	0.279
	5	3.28	146.1	2.14		37.3	0.288
	6	3.15	177	1.69		24.3	0.188
	7	3.51	193.3	1.73		25.3	0.196
HH #1, Female 58.64 kg	-3	1.43	208.7	0.653	0.57	--	--
	-2	1.04	173.3	0.572		--	--
	-1	<LOQ	187.6	0.267		--	--
	1	4.13	179.3	2.19		47.4	0.808
	2	3.49	172.2	1.93		39.7	0.677
	3	1.72	210.4	0.78		6.05	0.103
	4	28.5[6]	98.8	27.5		786	**13.4**
	5	11.8[6]	233.9	4.80		124	2.11
	6	2.21	132.4	1.59		29.7	0.507
	7	1.67	190.6	0.834		7.68	0.131
HH #3, Female, 104.55 kg	-3	2.68	86.5	2.95	2.50	--	--
	-2	6.51	285.6	2.17		--	--
	-1	6.97	265.2	2.50		--	--
	1	11.9	152.2	7.45		144	1.38
	2	12.2	165.7	7.01		132	1.26
	3	12.5	140.1	8.50		175	**1.67**
	4	16	269.9	5.65		91.8	0.878
	5	5.19	122.1	4.05		45.1	0.432
	6	6.69	172.7	3.69		34.6	0.331
	7	4.57	117.9	3.69		34.7	0.332
HH #4 Male 97.73 kg	-3	<LOQ	107.6	0.79	0.74	--	--
	-2	<LOQ	115.5	0.74		--	--
	-1	<LOQ	117.9	0.72		--	--
	1	3.74	158.6	3.82		90.0	0.921
	2	3.48	91.2	6.18		159	1.63
	3	8.07	199.8	6.54		169	1.73
	4	2.48	79	5.08		127	1.30
	5	6.53	112	9.44		254	2.60
	6	3.69	62.4	9.57		258	**2.64**
	7	4.47	180.3	4.01		95.7	0.980
HH # 6, Female, 118.18 kg	-3	<LOQ	42.8	1.17	1.17	--	--
	-2	<LOQ	45.6	1.10		--	--
	-1	1.31	52.1	2.39		--	--
	1	2.61	44.8	5.55		128	1.08
	2	4.21	57.4	6.99		170	1.44
	3	15.3[6]	47.2	30.9		868	**7.34**
	4	1.99[6]	38.4	4.94		110	0.931
	5	2.67	61.7	4.12		86.2	0.730
	6	7.67	112.5	6.49		156	1.32
	7	2.03	50.5	3.83		77.7	0.657
HH #7,	-3	2.21	164.4	1.28	1.15	--	--

Table 10. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Adults							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine correction (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
Female, 106.82 kg	-2	1.12	92.8	1.15		--	--
	-1	<LOQ	200.4	0.250		--	--
	1	1.25	146.6	0.812		-9.85	0
	2	1.72	173.4	0.945		-5.98	0
	3	3.02	194.7	1.48		9.57	0.0896
	4	4.19	162.8	2.45		38.0	0.356
	5	4.24	164.4	2.46		38.2	0.357
	6	1.55	94.2	1.57		12.2	0.114
	7	3.45	106.2	3.09		56.8	**0.532**
HH # 8, Female 150 kg	-3	Not Sampled			0.25	--	--
	-2	<LOQ	212.3	0.236		--	--
	-1	<LOQ	194.1	0.258		--	--
	1	<LOQ	315.8	0.158		-2.577	0.000
	2	5.04	172	2.79		74.3	**0.495**
	3	3.61[6]	255	1.35		32.2	0.215
	4	3.17	162.1	1.86		47.2	0.315
	5	4.83	239.2	1.92		49.0	0.326
	6	3.68	258.5	1.36		32.4	0.216
	7	2.05	177.2	1.10		25.0	0.167
	8	2.6	195.6	1.25		29.4	0.196
HH #9, Female 49.09 kg	-3	1.68[6]	195.2	0.82	3.09	--	--
	-2	5.99[6]	184.9	3.09		--	--
	-1	5.52[6]	85.3	6.16		--	--
	1	3.81	146.3	2.48		-17.672	0
	2	3.11	132.1	2.24		-24.625	0
	3	6.12	175.7	3.32		6.78	0.138
	4	5.63	155.2	3.45		10.8	0.220
	5	16.3	97.2	16.0		376	**7.67**
	6	8.07	200.2	3.84		22.0	0.448
	7	3.4	91	3.56		13.8	0.281
HH #10, Female 50 kg	-3	1.15	70.3	1.56	1.02	--	--
	-2	<LOQ	49.2	1.02		--	--
	-1	<LOQ	73.9	0.68		--	--
	1	1.96	85.3	2.19		34.2	0.685
	2	3.06	76.3	3.82		81.9	1.64
	3	1.99	39.5	4.80		110	2.21
	4	8.56	87.6	9.31		242	4.84
	5	4.72	48.9	9.19		239	4.78
	6	5.78	46.1	11.9		319	6.38
	7	6.89	50.1	13.1		353	**7.06**
HH #11, Female 65 kg	-3	<LOQ	105.4	0.474	0.68	--	--
	-2	1.27	176.7	0.685		--	--
	-1	1.41	177.9	0.755		--	--
	1	13.2	78.1	16.1		450	**6.92**
	2	3.25	103.6	2.99		67.3	1.03
	3	2.71	194.1	1.33		18.8	0.290
	4	5.08	188.1	2.57		55.1	0.848
	5	6.69	322.2	1.98		37.8	0.581
	6	2.55	129.8	1.87		34.7	0.533
	7	4.7	199.1	2.25		45.7	0.703
HH #14,	-3	<LOQ	66.1	0.76	1.25	--	--

Table 10. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Adults							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine correction (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
Female 68.18 kg	-2	1.3	90.2	1.37		--	--
	-1	1.02	77.9	1.25		--	--
	1	3.66	94	3.71		71.9	1.05
	2	17.3	80.6	20.4		561	**8.22**
	3	4.95	45.2	10.4		268	3.93
	4	4.83	47.5	9.68		246	3.61
	5	5.53	98.6	5.34		120	1.75
	6	4.54	52.6	8.22		204	2.99
	7	2.75	56.4	4.64		99.2	1.46
HH #15 Male 97.73 kg	-3	<LOQ	56.2	1.51	1.45	--	--
	-2	<LOQ	162.9	0.522		--	--
	-1	1.03	114.7	1.45		--	--
	1	1.25	157.4	1.29		-4.9	0
	2	<LOQ	62	1.37		-2.4	0
	3	1.94	81.6	3.85		70.0	0.716
	4	1.3	68.4	3.08		47.4	0.485
	5	1.33	79.4	2.71		36.7	0.376
	6	2.28	86.7	4.26		81.9	0.838
	7	4.66	135.5	5.57		120	**1.23**
HH #16, Female 100 kg	-3	<LOQ	115.7	0.432	0.43	--	--
	-2	<LOQ	213.9	0.234		--	--
	-1	3.04	95.4	3.03		--	--
	1	1.13	109.1	0.986		16.2	0.162
	2	<LOQ	104.9	0.477		1.30	0.0130
	3	<LOQ	101.9	0.491		1.71	0.0171
	4	<LOQ	50.4	0.992		16.4	**0.164**
	5	<LOQ	64.9	0.770		9.88	0.0988
	6	<LOQ	104.5	0.478		1.35	0.0135
	7	<LOQ	147.4	0.339		-2.71	0
HH #17, Female 65.91 kg	-3	<LOQ	87.1	0.574	0.41	--	--
	-2	<LOQ	160.4	0.312		--	--
	-1	<LOQ	122.4	0.408		--	--
	1	1.39	157.5	0.841		12.6	**0.191**
	2	<LOQ	117.1	0.427		0.540	0.0082
	3	<LOQ	161.6	0.309		-2.89	0
	4	<LOQ	67.7	0.739		9.64	0.146
	5	<LOQ	85	0.588		5.25	0.080
	6	<LOQ	118.2	0.423		0.424	0.0064
	7	<LOQ	85	0.588		5.25	0.080
HH #18, , Female 64.55 kg	-3	<LOQ	135.8	0.368	0.42	--	--
	-2	<LOQ	119.9	0.417		--	--
	-1	3.31	218.2	1.44		--	--
	1	6.38	116.2	5.23		141	2.18
	2	8.52	113.7	7.14		196	3.04
	3	26.1[6]	199.3	12.5		352	5.45
	4	20.7	139.2	14.2		401	**6.22**
	5	20.1	217.4	8.81		245	3.80
	6	7.88	166.7	4.50		119	1.85
	7	9.72	143.4	6.46		176	2.73
HH #20, Female	-3	<LOQ	91.6	0.55	0.84	--	--
	-2	<LOQ	59.6	0.84		--	--

Table 10. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Adults							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine correction (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
65.91 kg	-1	<LOQ	59	0.85		--	--
	1	4.03	85.2	4.50		107	1.62
	2	4.65	122.6	3.61		81.0	1.23
	3	2.1	65.4	3.06		64.8	0.983
	4	3.84	74.8	4.89		118	1.79
	5	15.5	123.9	11.9		323	**4.91**
	6	3.32	96.2	3.29		71.5	1.08
	7	3.41	108.5	2.99		62.9	0.955
HH #22, , Female 50 kg	-3	16.8	96.8	16.5	15.83	--	--
	-2	17.4	104.7	15.8		--	--
	-1	10.5	80	12.5		--	--
	1	9.38	71.1	12.6		-95.3	0
	2	119	44.6	254		6959	**139**
	3	21.8	58.6	35.4		572	11.4
	4	37	142.6	24.7		259	5.2
	5	34.8	155.8	21.3		159	3.2
	6	169	175.1	91.9		2222	44.4
	7	19.7	58.6	32.0		473	9.46
HH #24, Female 62.73 kg	-3	2.01	222	0.871	0.84	--	--
	-2	1.07	120.7	0.844		--	--
	-1	1.48	186.6	0.76		--	--
	1	7.48	195.4	3.65		81.8	1.30
	2	12.3	187.2	6.26		158	2.52
	3	17.4	194.4	8.52		224	**3.58**
	4	18	201	8.53		224	3.58
	5	18.9	267.1	6.74		172	2.74
	6	16.6	289	5.47		135	2.15
	7	12.5	214.1	5.56		138	2.20
HH #26, Female 104.55 kg	-3[8]	3.3	205.3	1.53	1.76	--	--
	-2[8]	2.73	143.8	1.81		--	--
	-1[8]	3.04	164.3	1.76		--	--
	1	2.5	234.2	1.02		-21.8	0
	2	8.9	219.1	3.87		61.5	0.588
	3	24.9	230.6	10.3		249	2.38
	4	52.7	274.6	18.3		482	**4.61**
	5	25.7	262.2	9.33		221	2.12
	6	7.87	176.8	4.24		72.3	0.692
	7	17.9	219.1	7.78		176	1.68
HH #27, Female 52.73 kg	-3	44.4	88.4	47.8	47.77	--	--
	-2	41.1	89.9	43.5		--	--
	-1	62.4	124.4	47.8		--	--
	1	52.7	95.2	52.7		145	2.74
	2	36.4	60.5	57.3		278	5.28
	3	51.1	79.9	60.9		384	7.28
	4	62.1	91.4	64.7		495	9.38
	5	49	75.3	62.0		415	7.87
	6	41.7	63.2	62.8		440	8.35
	7	72.3	100.6	68.4		604	**11.5**
HH #28, Female 50 kg	-3	16.7	199.5	8.05	6.96	--	--
	-2	9.83	134.5	6.96		--	--
	-1	9.97	145.3	6.53		--	--

Table 10. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Adults							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine correction (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
	1	26.3	122.9	20.4		392	7.84
	2	24	120.9	18.9		349	**6.98**
	3	30.5	153.6	18.9		349	**6.98**
	4	42.4	218.9	18.4		335	6.71
	5	16.5	114.6	13.7		197	3.94
	6	9.99	97.1	9.80		82.9	1.66
	7	5.89	50.2	11.2		123	2.46
HH #29, Female 68.18 kg	-3	1.29	380	0.32	0.33	--	--
	-2	<LOQ	142	0.35		--	--
	-1	<LOQ	150.6	0.33		--	--
	1	9.4	236.2	3.79		101	1.48
	2	39.4	111.1	33.8		977	**14.3**
	3	44	205.2	20.4		587	8.61
	4	50.9	263.7	18.4		527	7.73
	5	37.7	224	16.0		458	6.72
	6	28.7	174.4	15.7		448	6.57
	7	37.4	248.8	14.3		408	5.99
HH #30, Female 61.36 kg	-3	1.03	166.6	0.59	0.52	--	--
	-2	<LOQ	51.8	0.97		--	--
	-1	<LOQ	79.8	0.63		--	--
	1	<LOQ	142.2	0.352		-4.92	0
	2	<LOQ	64.1	0.780		7.59	**0.124**
	3	<LOQ	98.9	0.506		-0.43	0
	4	<LOQ	120.7	0.414		-3.09	0
	5	<LOQ	160	0.313		-6.06	0
	6	<LOQ	93.5	0.535		0.426	0.007
	7	<LOQ	107.9	0.463		-1.66	0
HH #31, Female 50.91 kg	-3	1.24	38.9	3.04	3.57	--	--
	-2	<LOQ	14	3.57		--	--
	-1	167	120.1	132		--	--
	1	14.6	66.7	20.8		505	**9.91**
	2	8.14	126	6.15		75.4	1.48
	3	<LOQ	18.7	2.67		-26.2	0
	4	<LOQ	14	3.57		0	0
	5	<LOQ	27.6	1.81		-51.4	0
	6	2.62	31.9	7.82		124	2.44
	7	9.49	129.1	7.00		100	1.97
HH #32, Female 67.27 kg	-3	<LOQ	65.6	0.76	1.00	--	--
	-2	<LOQ	50.1	1.00		--	--
	-1	<LOQ	56	0.89		--	--
	1	13.7	79.6	16.4		450	6.68
	2	10.8	54.5	18.9		522	**7.76**
	3	6.91	65.4	10.1		265	3.94
	4	13.5	73.3	17.5		483	7.18
	5	8.04	42.4	18.1		498	7.41
	6	3.57	47.5	7.16		180	2.67
	7	3.62	44.3	7.78		198	2.95
HH #33, Female 77.27 kg	-3	<LOQ	23.5	2.13	2.70	--	--
	-2	<LOQ	17.4	2.87		--	--
	-1	<LOQ	14	3.57		--	--
	1	<LOQ	24	2.08		-18.1	0

Table 10. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Adults							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine correction (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
	2	<LOQ	17.9	2.79		2.65	0.0342
	3	<LOQ	17.7	2.82		3.57	0.0462
	4	<LOQ	18.5	2.70		0	0
	5	<LOQ	18.5	2.70		0	0
	6	<LOQ	36.5	1.37		-38.9	0
	7	<LOQ	35.5	1.41		-37.8	0
HH #34, Female 80.91 kg	-3	1.43	234.8	0.580	0.58	--	--
	-2	1.62	209.6	0.736		--	--
	-1	1.31	214.9	0.581		--	--
	1	2.97	215.9	1.31		21.3	0.263
	2	1.31	162.2	0.769		5.51	0.068
	3	8.33[6]	73	10.9		300	**3.71**
	4	1.11	179.4	0.589		0.25	0.003
	5	1.18	147.1	0.764		5.36	0.066
	6	2.09	220.3	0.904		9.43	0.117
	7	3.81	330.6	1.10		15.1	0.187
HH #35, Female 86.36 kg	-3	Not Sampled			2.34	--	--
	-2	7.98	265.2	2.87		--	--
	-1	4.28	225.4	1.81		--	--
	1	2.48	100	2.36		0.725	0.0084
	2	4.19	190.7	2.09		-7.14	0
	3	2.93	51.5	5.42		90.0	1.04
	4	6.5	139.1	4.45		61.7	0.715
	5	6.35	155.7	3.88		45.2	0.523
	6	3.56	121.3	2.80		13.4	0.155
	7	3.43	147	2.22		-3.35	0
	8	38.5	113.7	32.2		874	**10.1**
HH #36, Female 81.82 kg	-3	2.6	176.5	1.40	1.40	--	--
	-2	3.59	244.2	1.40		--	--
	-1	7.92	209.7	3.60		--	--
	1	3.6	163.7	2.09		20.2	0.247
	2	8.33	275.8	2.88		43.0	0.526
	3	7.41	215.5	3.27		54.7	0.668
	4	84.8	235	34.4		963	**11.8**
	5	16	154.8	9.84		247	3.01
	6	13.1	185.7	6.72		155	1.90
	7	12.8	211.5	5.76		127	1.56
HH #37, Female 60.45 kg	-3	1.82	136.8	1.27	0.54	--	--
	-2	<LOQ	91.8	0.545		--	--
	-1	<LOQ	113	0.442		--	--
	1	24.4	131.1	17.7		502	**8.30**
	2	7.7	124.3	5.90		156	2.59
	3	5[6]	107.1	4.45		114	1.88
	4	3.58	107	3.19		77.2	1.28
	5	9.62	133.6	6.86		184	3.05
	6	4.71	181.1	2.48		56.4	0.934
	7	Not sampled					
HH #38, Female 56.82 kg	-3	7.05	280.8	2.39	2.51	--	--
	-2	5.85	208.7	2.67		--	--
	-1	4.09	155.3	2.51		--	--
	1	6.42	135.9	4.50		58.1	**1.02**

Table 10. Urinary 3-PBA levels and Absorbed Cyphenothrin Dose Estimates in Adults							
Study Participant	Study Day	Urinary 3-PBA (ng/mL)[1]	Urinary Creatinine (mg/dL)	Daily urinary 3-PBA, with field fortification and creatinine correction (µg/day)[2]	Background Urinary 3-PBA (µg)[3]	Absorbed Cyphenothrin Exposure (µg/day)[4]	Absorbed Cyphenothrin Dose (µg/kg/day)[5]
	2	9.8	215.1	4.34		53.5	0.941
	3	6.31	168.8	3.56		30.7	0.541
	4	5.81	152.5	3.63		32.7	0.576
	5	4.45	129.9	3.26		22.0	0.388
	6	1.01	34.9	2.76		7.24	0.127
	7	6.36	142.1	4.22		50.1	0.881
HH #39, Female 61.82 kg	-3	1.13	72	1.49	0.51	--	--
	-2	<LOQ	98.8	0.506		--	--
	-1	<LOQ	101	0.495		--	--
	1	<LOQ	109.4	0.457		-1.43	0
	2	2.21	146.4	1.44		27.2	0.440
	3	6.41	150.9	4.05		103	1.67
	4	5.81	180.9	3.06		74.6	1.21
	5	8.7	110.3	7.51		205	3.31
	6	26.6	126.9	20.0		568	**9.19**
	7	5.65	84.4	6.38		171	2.77
HH #40, Female 63.64 kg	-3	<LOQ	149.5	0.334	0.34	--	--
	-2	<LOQ	140.7	0.355		--	--
	-1	1.67	227.2	0.700		--	--
	1	<LOQ	175.3	0.285		-1.55	0
	2	<LOQ	146.2	0.342		0.110	0
	3	<LOQ	156.1	0.320		-0.523	0
	4	1.52	166.8	0.868		15.5	**0.243**
	5	<LOQ	207.2	0.241		-2.83	0
	6	1.05	214.7	0.466		3.72	0.059
	7	<LOQ	195.1	0.256		-2.39	0

All households applied a 40% ai product, except for HH #37 and #40 which applied a 20% ai product. The amount applied was dependant on the weight of the dog treated.

1. First morning void urine samples were analyzed. LOQ = 1.00 ng/mL. Residues <LOQ were assigned a value of ½ LOQ for calculation purposes.
2. Urinary 3-PBA (µg/day) = [3-PBA concentration corrected for field fortification (ng/mL) / measured creatinine (mg/dL) * 1 g/1000 mg * 1 dL/100 mL] * expected creatinine (g/day) *1 µg/1000 ng. 3-PBA concentrations were corrected using an average field fortification recovery of 105%. Expected creatinine values assumed by the study authors are: 1 g/day for females and 1.7 g/day for males.
3. Background 3-PBA (µg) = the minimum of either 1) median of the pre-treatment samples or 2) median of all sampling days.
4. Absorbed Cyphenothrin exposure (µg/day) = [urinary 3-PBA (µg) – Background urinary 3-PBA (µg)] * [MW ratio (375/214)/((fraction cypermethin excreted as 3-PBA in humans (0.06)/fraction of cypermethrin excreted as 3-PBA in rat (0.07) *fraction of cyphenothrin excreted as 3-PBA in rats (0.1))] / fraction of cypermethrin expected to be excreted in 24 hours (0.7).
5. Absorbed Cyphenothrin dose (µg/kg/day) = Cyphenothrin exposure (µg/day)/ Bodyweight (kg). Bolded values are the maximum values. Negative values were assigned a value of zero for further calculation purposes (eg, averages).
6. Average of replicate analysis.

Table 11. Summary of Daily Absorbed Cyphenothrin Dose for Adults (Post-Treatment) (µg/kg/day)				
Study Participant	Minimum	Maximum	Average	Standard Deviation
HH #2	0.071	0.564	0.267	0.152
HH #1	0.103	13.4	2.53	4.84
HH #3	0.331	1.67	0.898	0.552
HH #4	0.921	2.64	1.69	0.706
HH #6	0.657	7.34	1.93	2.40
HH #7	0	0.532	0.207	0.207
HH #8	0	0.495	0.245	0.155
HH #9	0	7.67	1.25	2.83
HH #10	0.685	7.06	3.94	2.45
HH #11	0.290	6.92	1.56	2.38
HH #14	1.05	8.22	3.29	2.44
HH #15	0	1.23	0.521	0.448
HH #16	0	0.164	0.0668	0.0731
HH #17[1]	0	0.191	0.0731	0.0747
HH #18	1.85	6.22	3.30	1.58
HH #20	0.955	4.91	1.80	1.41
HH #22	0	139.2	30.4	50.2
HH #24	1.30	3.58	2.58	0.814
HH #26	0	4.61	1.72	1.54
HH #27	2.74	11.5	7.48	2.82
HH #28	1.66	7.84	5.22	2.49
HH #29	1.48	14.3	7.35	3.82
HH #30[1]	0	0.124	0.019	0.046
HH #31	0	9.91	2.26	3.53
HH #32	2.67	7.76	5.51	2.23
HH #33[1]	0	0.0462	0.0115	0.020
HH #34	0.0031	3.71	0.631	1.36
HH #35	0	10.1	1.57	3.47
HH #36	0.247	11.8	2.81	4.06
HH #37	0.934	8.30	3.01	2.71
HH #38	0.127	1.02	0.640	0.326
HH #39	0	9.19	2.66	3.11
HH #40	0	0.243	0.043	0.091
Overall				
Minimum	0	0.0462	0.0115	0.020
Maximum	2.74	139	30.4	50.2
Average	0.548	9.47	2.96	3.19
Standard Deviation	0.785	23.7	5.32	8.55

1. 3-PBA residues were <LOQ in all or all but one post-treatment urine sample (HH #17, 30, and 33)

Table 12. Summary of Daily Absorbed Cyphenotrhin Dose By Study Day for Adults (µg/kg/day)						
Study Day	n	Minimum	Maximum	Average	Standard Deviation	Median
1	33	0	9.91	1.74	2.78	0.685
2	33	0	139	6.18	24.1	0.941
3	31	0	11.4	2.39	2.99	1.04
4	33	0	13.4	2.91	3.67	0.931
5	33	0	7.87	2.28	2.46	1.75
6	33	0	44.4	3.06	7.81	0.838
7	32	0	11.5	1.91	2.79	0.918
8	2	0	10.12	5.16	7.0	10.78

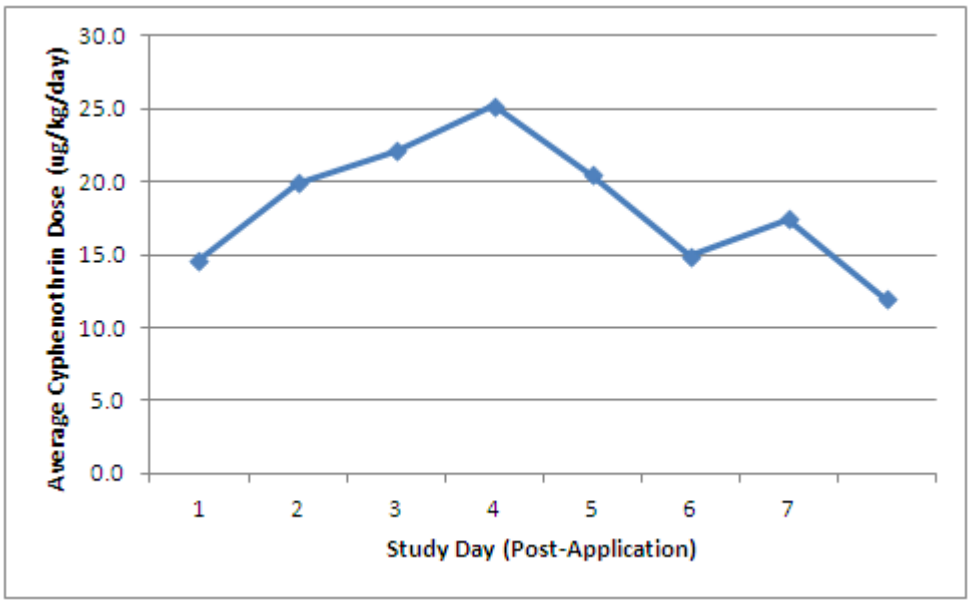

Figure 1. Graph of Average Absorbed Cyphenothrin Dose vs Study Day for Children

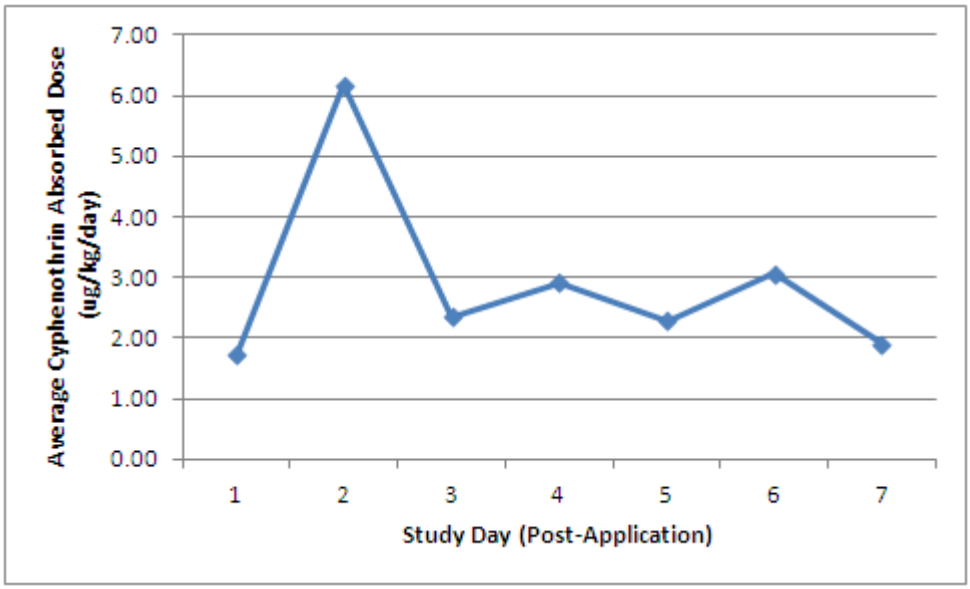

Figure 2. Graph of Average Absorbed Cyphenothrin Dose vs Study Day for Adults

References

Crawford, M.J., Croucher, A., Hutson, D.H. (1981). The metabolism of the pyrethroid insecticide cypermethrin in rats; Excreted metabolites. Pestic. Sci. 12: 399-411.

Kaneko, H., Matsuo, M., and Miyamoto, J. (1984). Comparative metabolism of sterioisomers of cyphenothrin and phenothrin isomers in rats. J. Pestic. Sci. 9: 237-247.

Woollen, B., Marsh, J., Laird W., and Lesser, J. (1992). The metabolism of cypermethrin in man: differences in urinary metabolite profiles following oral and dermal administration. Xenobiotica 22: 983-991.

MRID 41551102

APPENDIX A

Compliance Checklist for

"An Observational Biomonitoring Study for Measurement of Human Exposure to Cyphenothrin During and Following Application of Sergeant's Gold® Flea & Tick Squeeze-On for Dogs"

COMPLIANCE CHECKLIST

Compliance with OPPTS Series 875, Postapplication Occupational and Residential Exposure Test Guidelines, Group B: Guidelines, 875.2600 (Biological monitoring) is critical. The itemized checklist below describes compliance with the major technical aspects of OPPTS 875.2600.

- *The Agency requires investigators to submit protocols for review purposes prior to the inception of the study. Adequate pharmacokinetic data must exist to effectively interpret the data.* It is unsure if the protocol was submitted to EPA prior to the study inception.

- *Expected deviations from GLPs should be presented concurrently with any protocol deviations and their potential study impacts.* This criterion was met.

- *The test substance should be a typical end use product of the active ingredient.* This criterion was met.

- *The application rate used in the study should be provided and should be the maximum rate specified on the label. However, monitoring following application at a typical application rate may be more appropriate in certain cases.* This criterion was most likely met. The households applied the product in the manner they normally would, but were not monitored to ensure compliance with the product label.

- *Selected sites and seasonal timing of monitoring should be appropriate to the activity.* This criterion was met.

- *A sufficient number of replicates should be generated to address the exposure issues associated with the population of interest. Specifically, each study should include a minimum of 15 individuals (replicates) per activity.* This criterion was met.

- *Test subjects should be regular workers, volunteers trained in the work activities required, or typical homeowners*. This criterion was met.

- *The monitored activity should be representative of a typical working day for the specific task in order to capture all related exposure activities.* This criterion was met as it was an observational study.

- *The exposure monitoring period should be of sufficient length to ensure reasonable detectability of residues in biological media (e.g., blood and urine) consistent with pharmacokinetic data such as excretion profile, duration time, etc.* This criterion was met.

- *Biomonitoring should be conducted using methodologies based on the pharmacokinetic properties of the pesticide (parent compound and its metabolites) of concern (e.g., need validated pharmacokinetic models from humans or appropriate animal surrogate and appropriate route of exposure).* This criterion was partially met. The study author did

not account for the amount of cyphenothrin excreted per day.

- *Any protective clothing worn by study participants should be identified and should be consistent with the product label.* This criterion was partially met. No participants reported wearing protective clothing. All participants wore their normal clothing.

- *If urine monitoring is being conducted, urine samples should be collected one or two days before participating in the applicator exposure monitoring activities and should continue on the day of exposure and for an appropriate time period after these activities have been completed, depending on the excretion kinetics of the compound. The 24-hour sample collection cycle should begin with the first void after beginning work activities and end with the first void on the following morning, continuing this 24-hour cycle on subsequent days.* This criterion was not met, Only random urine samples were collected

- *If blood monitoring is being conducted, baseline blood samples should be collected from each individual prior to exposure. Based on pharmacokinetics, postapplication exposure samples should be collected at the appropriate times before, during, and after exposure.* This criterion is not applicable, blood was not collected.

- *Materials used for sample collection should not interfere with (e.g., absorb) the analytes of interest.* This criterion was met.

- *Creatinine levels should be determined as a way of qualitatively monitoring completeness of urine collection samples. Specific gravity, as another measure of 24-hour sample completeness, should be performed as soon after collection as possible (and before sample storage).* These criteria were partially met. Creatinine levels were determined; however, it was not reported if the specific gravity of the urine was analyzed.

- *Prior exposures to the test pesticide or structurally related compounds may interfere with study results. A brief history should be taken from each participant relating to known prior exposures to pesticides for at least the last 2 weeks, including reentry into potentially treated fields. For urine monitoring, there should also be a sufficient time period between such exposures and participation in the study to ensure adequate urinary clearance of the compound and its metabolites, based on pharmacokinetic data.* This criterion was partially met. A history was obtained for the study duration, but does not appear to have included the period prior to the pre-treatment sample collection.

- *Validated analytical methods for the biological analyte (parent compound and its metabolites) of sufficient sensitivity are needed. Information on method efficiency and limit of quantitation (LOQ) should be provided.* This criterion was met.

- *Samples should be stored in a manner that will minimize deterioration and loss of analytes between collection and analysis. Biological monitoring samples (e.g., serum, plasma and urine) should be refrigerated or stored frozen prior to analysis. Whole blood should not be frozen. Information on storage stability should be provided.* This criterion was met.

- *Data should be corrected if any appropriate field fortified, laboratory fortified or storage stability recovery is less than 90 percent.* Overall average recovery of all field fortification samples was 105%. The study author did not correct for field fortification

recovery.

- *Unless stability of the analyte has been established prior to initiation of the study, three samples of control (nonparticipant) should be fortified with two levels of the biological analyte (parent or metabolite(s), whichever is appropriate) for each experimental site.* This criterion was partially met. Field fortification samples were prepared at RTI and shipped with each shipment of samples.

Each subject's absorbed dose should be expressed in terms of body weight using his/her own measured value, and as a cumulative total for each exposure period. The arithmetic mean, range, standard deviation, and coefficient of variation should be calculated from the results of all individuals. Geometric mean, range and standard deviation may be calculated if the results are shown to be log-normally distributed. Other distributional data should be reported, to the extent possible (e.g., percentiles). These criteria were partially met. Absorbed daily doses were calculate daily, however results were not shown cumulatively